CASE STUDIES IN CLINICAL APPLICATIONS OF THERAPEUTIC PLASMA EXCHANGE

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Objectives

- Explain the process of a therapeutic plasma exchange (TPE).
- List possible complications of TPE.
- List possible indications for TPE as defined by AABB.
- Explain benefits of TPE in antibody-mediated pathologies found in two cases.
What we will discuss today

- Introduction and definition of Therapeutic Plasma Exchange (TPE)
- Applications of TPE, including AABB indications.
- Case 1: Stem Cell Transplantation
- Case 2: Autoimmune Hemolytic Anemia with monoclonal gammopathy.
- Questions, References, and Conclusion
What is a Therapeutic Plasma Exchange?

- Procedure (done by apheresis) to remove and retain the patient’s plasma while returning cellular components to patient.
  - Usually replacing the plasma volume with a similar substance, either donor plasma or albumin, or a mix of both.
  - When albumin is used, it is usually blended with saline, unless patient becomes hypotensive.
- Prevents large loss of RBC volume while allowing for filtration of plasma.

- Why do we want to do this to a patient?
Apheresis machine

Source: National Institutes of Health
Uses of TPE

• Used first around 1952 to treat plasma hyperviscosity related to multiple myeloma (Bobati & Naik, 2017).

• Several uses and applications today.
  • AABB breaks these uses down into indications by four categories, explained later on the slide.

• Complications can include reduced coagulation factor availability and lowered fibrinogen levels, both of which may require transfusion management.
TPE Indications (per the AABB Technical Manual)

• **Category I**: “Disorders for which apheresis is accepted as a first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.”
  - Examples: Myasthenia Gravis, Goodpasture syndrome, hyperviscosity in monoclonal gammopathies, ABO incompatibilities in certain transplants, and more.

• **Category II**: “Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.”
  - Examples: Major mismatch for stem cell transplantation, Antibody-mediated rejection of renal transplant, mushroom poisoning, and more.
• **Category III:** “Disorders in which the optimal role of apheresis therapy is not established. Decision-making for patients should be individualized.”
  - Examples: Autoantibody coagulation factor inhibitors, postpartum HELLP, Refractory immune thrombocytopenia, posttransfusion purpura, sepsis with multiorgan failure.

• **Category IV:** “Disorders in which published evidence demonstrates or suggests apheresis is ineffective or harmful. Institutional review board is desirable if apheresis treatment is undertaken in these circumstances.”
  - Examples: Lupus / SLE Nephritis, psoriasis, amyloidosis, antepartum HELLP.
Plasma exchanges at TUKHS

- Robust apheresis program for TPE, as well as WBC and RBC apheresis.
- Most at KU are done with albumin and saline, though some are done with undilute albumin (if patient becomes hypotensive).
- Less than 10% of cases are performed with donor plasma as the replacement.
- Increasing utilization:
  - 2015: 655 TPE cases
  - 2016: 801
  - 2017: 915
Case study 1

- Patient history: Leukemia patient following up post bone marrow transplantation four months ago.
  - Recipient: O Pos
  - Donor: A Neg
- Chronically anemic. 23 units pRBCs administered since transplantation, with increasing frequency, presenting with a 5.7 g/dL Hemoglobin today.
  - WBC count normal, suggesting myeloid engraftment.

<table>
<thead>
<tr>
<th>Anti-A</th>
<th>Anti-B</th>
<th>Anti-D</th>
<th>A1 Cells</th>
<th>B Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>4+</td>
</tr>
</tbody>
</table>

Where are our A Neg RBCs in the front type?
Case study 1: BMT, continued.

- **Major ABO Incompatibility** between recipient and donor.
- Supported with O Neg RBCs, but anti-A1 still detectable in plasma, and no evidence of BMT donor being a subtype.
- Think: What would support the lack of complete conversion of blood type and the patient’s chronic anemia?

*Major ABO incompatibility* is defined as the presence of isoagglutinins in the recipient against a donor’s A or B blood group antigens (Schwartz, et al., 2016)
Major ABO Incompatibility

- Serologically, we detected an antibody against the A antigen.
- This antibody has persisted even after the donor marrow has (mostly) engrafted.
- According to literature, persistent isoagglutinins against A or B antigens can delay RBC engraftment and destroy erythroid precursors, leading to pure RBC aplasia (Schwartz, et al., 2016)
  - Fits our patient, who has detectable anti-A in the backtype and is increasingly transfusion dependent.
- Isohemagglutinin titer performed:
  - Anti-A, 1:32
Case 1: Treated with therapeutic plasma exchange

<table>
<thead>
<tr>
<th></th>
<th>On Admission</th>
<th>After 2x Plasma Exchange</th>
<th>Most Recent Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Type</td>
<td>O Neg*</td>
<td>O Neg*</td>
<td>A Neg</td>
</tr>
<tr>
<td>Isohemagglutinin Titer</td>
<td>1:32</td>
<td>1:4</td>
<td>Not done</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>5.7 g/dL</td>
<td>7.1 g/dL</td>
<td>12.2 g/dL</td>
</tr>
</tbody>
</table>

*- Resulted as “No Type Determined” due to incomplete transition to donor type
Case study 2

- Patient history: newly diagnosed lymphoma, Type 2 Diabetes, Acute Kidney Failure.

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Patient Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>5.0 g/dL</td>
<td>13.5-16.5 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>15.9%</td>
<td>40%-50%</td>
</tr>
<tr>
<td>Reticulocyte %</td>
<td>1.5% (uncorrected)</td>
<td>0.5%-2.0%</td>
</tr>
<tr>
<td></td>
<td>0.5% (corrected)</td>
<td></td>
</tr>
<tr>
<td>Absolute Reticulocyte Count</td>
<td>5.9 x 10³/uL</td>
<td>30-94 x 10³/uL</td>
</tr>
</tbody>
</table>
Case study 2, continued

**Blood Bank Results, Type and Screen**

<table>
<thead>
<tr>
<th></th>
<th>Anti-A</th>
<th>Anti-B</th>
<th>Anti-D</th>
<th>Mono Control</th>
<th>A1 Cells</th>
<th>B Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Gel SC I</th>
<th>Gel SC II</th>
<th>Gel AC</th>
<th>Solid Phase SC I</th>
<th>Solid Phase SC II</th>
<th>Solid Phase SC III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3+mf</td>
<td>3+mf</td>
<td>3+mf</td>
<td>4+</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>
Case study 2, continued

- Blood Bank Results, DAT

<table>
<thead>
<tr>
<th></th>
<th>Poly</th>
<th>Anti-IgG</th>
<th>Anti-C₃b, -C₃d</th>
<th>Saline Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
</tr>
</tbody>
</table>

- Antibody workup resulted in no specificity
- Cold agglutinin present
- Warm washing cells performed to resolve type and DAT discrepancies.
Case study 2, continued

- Blood Bank Results, Warm Washed RBCs used, Type I DAT

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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>ND</td>
<td>4+</td>
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</tr>
</thead>
<tbody>
<tr>
<td>2+</td>
<td>(+)</td>
<td>2+</td>
<td>0/0</td>
</tr>
</tbody>
</table>

- Serologic findings: Indeterminate antibody present (warm and cold autoantibodies identified, referred out for alloadsorption and further evaluation).
- Prewarm techniques seem to circumvent reactivity with unit crossmatches.
Case study 2, cold agglutinin

- Micrograph from peripheral smear
Case study 2, patient background, cont.

- Admitted 24 days ago to outside facility with critically low hemoglobin (4.1 g/dL).
  - 5 units pRBCs given, hemoglobin 7.2, discharged after a short stay.

- Admitted to another facility yesterday, noted to have hemolytic anemia and severe rouleaux.
  - Given immunosuppressants and folate
  - Transferred to TUKHS for evaluation of lymphoma and management of autoimmune hemolytic anemia

- On admission, further laboratory evaluation performed.
Case 2: Additional Labs

- IgG normal, IgA normal, but IgM above analytical range (>5000 mg/dL, normal 38-328).
- Reference lab cold agglutinin titer
  - 1:524288 (reference range 1:32)
- Protein electrophoresis
  - Elevated total serum protein (11.3 g/dL, ref 6.0-8.0)
  - Low albumin fraction (27.6%, normal 48-68%)
  - Beta/Gamma spike
Case 2: Piecing it all together…

- Likely as a result of patient’s lymphoma, we are dealing with a (at least debatably) clinically significant cold autoantibody, along with a warm autoantibody we eluted off the RBCs (no allos, both cold and warm auto confirmed by our reference lab).
- Transfusion approach: Use blood warmers, keep patient warm to minimize impact of cold agglutinin, use prewarm technique when crossmatching units – units ended up compatible.
- Clinicians attempted to treat autoimmune response with multiple immunosuppressants, but patient was critically ill with severe anemia.
Case 2: TPE Time!

- Patient received two TPEs with albumin- first on day of admission, another a week later.
- IgM prior >5000, post TPE 1: IgM 2880 mg/dL
- IgM trended back up to 4800 mg/dL by day 6 after admission
- IgM reduced to 3260 mg/dL after second plasma exchange.
- Patient only required one unit pRBCs after both plasma exchanges- hemolytic anemia stymied.

- Patient was discharged and follows up with a clinician outside of our system.
Conclusion

- As evidenced in both cases, plasma exchanges can impact the blood bank in a variety of ways.
  - Our serological testing can be impacted by the pathologies these patients present.
  - We may be called upon to provide plasma either as the basis of the exchange or to replace depleted coagulation factors and fibrinogen.
- These cases represent just a couple of the many conditions treated by therapeutic plasma exchange.
- A transfusion service and lab may have to support these cases in more ways than just administering cryo or plasma on a rare occasion.
  - For example, our use of isohemagglutinin titers, serum IgM levels, and more.

- Questions?
  - Big thank you to Dr. Plapp at KU for his guidance in gathering material for this presentation today.
References

